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TITLE: Natural Sensation of Foot-Floor Interactions for Trans-femoral Amputees via Neural Stimulation

PRINCIPAL INVESTIGATOR: Ronald Triolo, PhD

CONTRACTING ORGANIZATION: Louis Stokes Cleveland VA Medical Research & Education Foundation, Cleveland, OH

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14. ABSTRACT
The objective of this project is to provide useful sensation of prosthetic foot-floor interactions to trans-femoral amputees by directly interfacing with the nervous system in the residuum. Amputees are slow to adapt to loss of lower limb sensation, and fall-related fear and anxiety are all life-long consequences of amputation. Over this reporting period, we have identified and enrolled a 50-year-old Army Veteran with a left knee disarticulation who will be our first implant recipient. Our technical and clinical teams have worked to develop a surgical plan in which the ideal incision locations for the internal connectors and percutaneous exit sites were determined. We anticipate the implant surgery to be completed by the end of 2021. Furthermore, we have accessed and streamed internal sensor data from the Genium prosthesis in real time, and finalized the integration of the signals with our external stimulator controller. This completed the proposed elements of the sensory neuroprosthesis that will provide users with sensations of foot-floor interactions as well as the knee joint angle. We have expanded their outreach and are actively working to identify new potential sources of participant referrals by contacting clinicians and prosthetists both locally and nationally. Psychometric and functional test continues with previously enrolled transtibial participants.

15. SUBJECT TERMS

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1. INTRODUCTION:

The objective of this project is to provide useful sensation of prosthetic foot-floor interactions to trans-femoral amputees by directly interfacing with the nervous system in the residuum. Amputees are slow to adapt to loss of lower limb sensation, and fall-related fear and anxiety are all life-long consequences of amputation. These issues are particularly important for individuals with trans-femoral limb loss who constitute approximately 40% of the entire amputee population. Despite noteworthy advances in robotic prostheses for lower limb amputees, meaningful and direct sensory feedback from the lost limb has not yet been incorporated into currently available prosthetic technologies. This project focuses on restoring useful sensation of prosthetic foot-floor interactions as well as knee joint motion to trans-femoral amputees by directly exciting the upper sciatic nerves remaining in the residual limb with the new, non-penetrating, high contact density Composite Flat Nerve Interface Nerve Electrode (C-FINE). We hypothesize that the electrically evoked sensations from C-FINEs implanted on the proximal sciatic nerve in the residuum will be perceived as naturally arising from the missing limb, that their psychometric properties (quality, location, modality and intensity) will be stable, and that they will improve standing balance, gait mechanics and symmetry, and the ability to negotiate unstructured terrain and uneven surfaces. Positive effects on the cognitive attention required for walking in unfamiliar or distracting environments, incidence and fear of falling, balance confidence, and phantom pain are also anticipated and will be reflected in patterns of home and community use.

2. KEYWORDS:

Sensory restoration, lower-limb amputees, nerve cuff electrodes, peripheral nerve stimulation, gait, balance, sensory neuroprosthesis

3. ACCOMPLISHMENTS:

What were the major goals of the project?

During this project we aim to:
1) Design, prototype, verify and produce new hardware and software to extract sensor signals from an advanced microprocessor-controlled knee and utilize them to control neural stimulation. (90% Completed).
2) Identify five trans-femoral amputees and install high contact density C-FINEs on their proximal femoral nerves. (20% Completed). Expected implant date for the first subject: December 2021
3) Characterize psychometric properties and explore interactions between perceived sensation and all system inputs. (Will begin after implantation of our first subject with trans-femoral limb loss. Our mitigation plan is to continue to pursue this work with 3 transtibial amputees who previously received identical implanted systems under separate DoD funding.)
4) Determine effects of natural sensation on standing balance, gait mechanics, stair/ramp ascent and negotiating difficult terrain under various conditions. (Will begin after implantation of our first

subject with trans-femoral limb loss. Our mitigation plan is to continue to pursue this work with 3 transtibial amputees who previously received identical implanted systems under separate DoD funding.)
5) Explore subjective perceptions of balance confidence, utility, comfort, satisfaction and ease of use of the sensory neuroprosthesis and measure effects on cognitive/attentional burden and incidence/severity of falls and phantom pain episodes. (Will begin after implantation of our first with trans-femoral limb loss. Our mitigation plan is to continue to pursue this work with 3 transtibial amputees who previously received identical implanted systems under separate DoD funding.)

What was accomplished under these goals?

Major Clinical Accomplishments

We recently identified and enrolled a 50-year-old Army Veteran with a left knee disarticulation who lost his limb three years ago in a motor vehicle accident. He is a daily user of an ALUX Microprocessor Knee and is very interested in participating in the study. We have completed all the screening assessments, thoroughly examined his residual limb, and inspected pressure points on the socket to determine suitable incision sites for the implanted system. He has signed the consent form for implant surgery, and we have devised and refined a surgical plan with the vascular surgeon on the team (Co-Investigator Dr. Gilles Pinault) who will perform the operation. This will be our first implantation surgery for this project. We are actively working with the surgeon and the clinical staff at the Louis Stokes Cleveland VA Medical Center (LSCVAMC) to secure an OR date. We anticipate that the implant surgery will be completed before the end of 2021.

Although identifying and enrolling new participants have been challenging due to the ongoing COVID-19 pandemic, we have updated our recruitment plan to expand our outreach and informing the amputee community about the study. We have produced high-quality prints of our IRB approved informational flyer, which has been distributed to local prosthetists, physical therapists, and amputee support groups. Moreover, we have worked with a professional medical illustrator at the Advanced Platform Technology Center (APTC) at LSCVAMC to create an illustration which will be published in the *Amputee Coalition* magazine as an advertisement to inform readers about the study and serve as another source of recruitment. This advertisement will be published after pending IRB approval. Furthermore, we have increased the media coverage of our project by inviting reporters and news programs to our laboratory to cover ongoing activities on this and other lower limb sensory restoration projects to inform the public about the study and potentially find interested candidates. One of such video reports has been already aired during The PBS NewsHour (see Dissemination Activities below for more details). The filming for two other mass market media reports (*SHOWTIME VICE* and *FOX8* Local News) were completed and they are in postproduction with expected airing within a few months from the submission date of this report. Finally, we have been in regular contact with the National Director of Amputee Health (Dr. Joseph Webster), Walter Reed National Military Medical Center (Dr. Paul Pasquina), the Tampa VA Medical Center (Dr. Jeffery Heckman), and OrthoCarolina (a private medical practice specializing in limb loss) to identify potential implant candidates.

Major Technical and Scientific Accomplishments

We developed and implemented a new firmware package for our external stimulator unit. This firmware ensures operational stability of the stimulation system and supports enhanced data logging capabilities required for home and community use of the sensory neuroprosthesis (SNP). In addition, we have designed and completed rigorous testing of a new cellphone-based interface to facilitate intuitive use of the SNP outside of the laboratory by system recipients. These software updates provide much easier, more reliable, and user-friendly communication between the stimulator and the instrumented prosthesis. The smartphone app allows users to adjust the stimulation intensity and length of stimulation within a previously specified safe range. The design and benchtop testing of the new firmware for the external stimulator and the app to control the SNP were performed under strict design controls and are fully documented in the APTC Quality System. We have also compiled the required documents for regulatory approval from the local IRB and the FDA. Upon completion of pending electromagnetic compatibility and electrical safety tests, we will amend to our existing IDE to incorporate these new technical system components Submission of the IDE amendment is expected within 2 months with approval approximately one moth afterwards.

We devised, implemented, and tested a method of wirelessly accessing the sensors for knee angle rate, axial load, and knee moment from the Genium microprocessor-controlled knee. The initial data collection was accomplished via a custom routine in MATLAB and a PC equipped with a Bluetooth receiver. Using this platform and custom microcontroller programming, we were able to successfully connect to the Genium device, initiate data transmission, receive sensor data, and document characteristics such as range, noise level, and packet loss rate of the wireless communication. To integrate the data stream with our external stimulator, we developed an embedded solution based on a Teensy 3.6 board equipped with a 180 MHz ARM Cortex-M4 processor and real-time capabilities. The Teensy board was interfaced wirelessly with the Genium prosthesis in real time. The received data were examined for integrity and processed to make them suitable for input to the stimulator control module which will modulate the pulse parameters based on the sensor signals.

To mitigate potential delays due to the ongoing COVID-19 pandemic which adversely affected our recruitment and implant surgery timeline, we continued to make progress on the elements outlined in the statement of work with transtibial amputees previously enrolled in this and other studies supported by the DoD. This has allowed us to continue investigating the effects of SNP in a similar target population (transtibial vs. transfemoral), and to complete the development of the new technology required for this project. We regularly perform experiments similar to the ones in the SOW with three previous recipients of the SNP system with transtibial limb loss. These experiments include thresholding and perceptual mapping, speed matching during split-belt treadmill walking, and determining reflex responses during and after sensory stimulation. Most notably during this reporting period, we completed an 11-month long homegoing trial with one of our SNP recipients with transtibial limb loss. He utilized the SNP on daily basis at home and in the community. During this trial, we conducted a series of planned subjective and functional assessments to ascertain how use of the SNP affects activities of daily living, phantom limb perception, pain level, and functional performance during walking and stair negotiation. Two submissions based on this work were accepted for presentation at the *International Society for Prosthetics and Orthotics (ISPO) 18th World Congress* which will happen on November 1-4, 2021. We are also completing a journal manuscript summarizing our findings from this homegoing trial (submission expected by the end of 2021). In addition, in February 2021, we published a manuscript, titled “Lower-Limb Amputees Adjust Quiet Stance in Response to Manipulations of

Plantar Sensation" in *Frontiers in Neuroscience*. This manuscript describes how manipulating plantar sensation in lower-limb amputees results in adjusting quiet stance. Our findings suggest that body's motor control system treats sensory inputs from peripheral nerve stimulation similarly to native tactile inputs.

Major Dissemination Accomplishments

Our team organized and moderated a session titled, "Sensorimotor Neuroprosthetics: Are We Ready for Widespread Clinical Application?" at the *Neural Interfaces Conference* on June 25, 2021. Leading researchers in the field presented their latest scientific findings, shared some of the challenges in sensory restoration techniques, and discussed future directions. Furthermore, Co-Investigator Dr. Hamid Charkhkar co-moderated a mini-symposium titled "Technologies to Restore Sensory Feedback after Lower-Limb Amputation" at the *10th International IEEE/EMBS Conference on Neural Engineering (NER'21)*. This special session consisted of six speakers and was jointly organized by Dr. Charkhkar and Dr. Lee Fisher from the University of Pittsburg. In addition, our work was featured on *The PBS NewsHour* on September 1, 2021. This coverage was part of the report entitled "How Sensors, Rewiring Nerves Could Help Prosthetics Feel and Function Like Real Limbs" produced by renowned reporter, Miles O'Brian.

What opportunities for training and professional development has the project provided?

All team members completed *DoN Human Research* training and *VA Human Subjects Protection and Good Clinical Practices* through Collaborative Institutional Training Initiative.

We have procured and installed a state-of-the-art real-time control rapid prototyping system (Speedgoat) in our laboratory that facilitates model-based design using MATLAB and Simulink. Students and technical staff have learned how to use this new system and can develop the code to control delivery of electrical stimulation to cuff electrodes based on acquired sensor signals and interface with peripheral hardware in real time.

With support from a special equipment grant from the Rehabilitation R&D Service of the US Department of Veterans Affairs, we acquired two new pieces of equipment for use in this project: 1) a Computerized Dynamic Posturography (CDP) device equipped with immersive virtual reality, and 2) an instrumented staircase (both from Bertec, Inc.). The CDP device enables us to characterize static and dynamic balance while ascertaining the relative contributions of different sensory inputs such as vision, proprioception and vestibular system. Drs. Charkhkar and Sheehan attended a training course to learn how to operate the CDP device and have instructed

other members of the staff in its use. The instrumented stairs are equipped with highly accurate forceplates designed to measure ground reaction forces while ascending or descending stairs. The delivery of this equipment is expected late October 2021 and all team members will be trained on how to configure the system and collect force, moment and center of pressure data during stair negotiation and mobility tasks.

How were the results disseminated to communities of interest?

We publish all our scientific findings in professional clinical/scientific venues that are Open Access to disseminate results and progress free of charge to the public. On February 2, 2021, we published an article in *Frontiers in Neuroscience* which described the results of manipulating plantar sensation in lower-limb amputees on adjusting quiet stance.

On August 3, 2021, we volunteered for the Virtual Internship Fireside Chats event which was hosted by Case-Coulter Translational Research Partnership (CCTRP) at Case Western Reserve University. During this event more than 100 attendees, mainly undergraduate students in biomedical engineering from across the country, learned about our project through a dynamic presentation and a follow up Q&A session.

To increase our outreach, we have worked with the medical illustrator at APTC to design a new illustration to inform the public about our study. This illustration will be part of an advertisement in *inMotion,* the magazine of The Amputee Coalition. This publication is issued bimonthly for amputees, caregivers and healthcare professionals, providing information related to limb loss.

In addition, our work was featured on *The PBS NewsHour* on September 1, 2021. This coverage was part of the report entitled "How Sensors, Rewiring Nerves Could Help Prosthetics Feel and Function Like Real Limbs" produced by renowned reporter, Miles O'Brian. The filming for two other reports, from *SHOWTIME VICE* program and *FOX 8* local TV channel*,* have been completed and they are in postproduction phases.

What do you plan to do during the next reporting period to accomplish the goals?

- Complete the implantation surgery for the first SNP recipient with trans-femoral limb loss
- Conduct threshold/mapping and functional experiments with the first trans-femoral participant
- Continue efforts to identify, recruit, screen, and enroll subsequent candidates with trans-femoral limb loss for the study
- Acquire approval from IRB and FDA for our new stimulator controller and the smartphone app

- Procure all the system components necessary for all planned implant surgeries
- Continue the psychometric and functional tests with previously enrolled participants with transtibial limb loss
- Start the 2nd homegoing trial with a system recipient with transtibial limb loss

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Our article published in *Frontiers of Neuroscience* examined how electrically elicited tactile input is incorporated into the body's sensorimotor system. Results from this work expanded the base of knowledge on how plantar tactile information is integrated with other sensory modalities to control postural adjustments during internally generated perturbations.

Upcoming presentations by our team members at the *International Society for Prosthetics and Orthotics (ISPO) 18th World Congress* will share, for the first time, the effects of the prolonged use of the SNP in a lower limb amputee. These findings are crucial to identify benefits as well as challenges in transitioning this technology outside the laboratory and into the real life.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Actual or anticipated problems or delays and actions or plans to resolve them

We experienced significant delays in identifying and enrolling participants during this reporting period due to the ongoing COVID-19 pandemic. For example, last year we had identified a female Veteran with trans-femoral limb loss who completed all screening tests, and formally enrolled in the study after signing all necessary informed consent documents. Implant surgery had been scheduled for October 2020. However, the candidate decided not to participate in the study due to COVID-19 concerns and other personal reasons. Therefore, some of the expected progress outlined in the last year's report did not materialize.

The newly enrolled participant, a 50-year-old Army Veteran with a left knee disarticulation, is very enthusiastic about the study and we expect to complete the implantation surgery by the end of 2021. Despite the completion of the screening process in early summer 2021, we are encountering some delays in securing OR time due to a backlog in elective procedures at Louis Stokes Cleveland VA Medical Center. Our team actively coordinates with the medical staff at LSCVAMC and the surgeon on the team to identify a suitable OR date for the implant procedure. Because of these unforeseen circumstances, the experimental schedule anticipated with participants with trans-femoral limb loss had to be adjusted accordingly. We are mitigating the impact of these issues by continuing to collect data from experiments described in our SOW with previous recipients of the implanted SNP who have transtibial limb loss.

To accelerate our recruitment effort, we have developed a plan which could be summarized by a) distributing our IRB approved study flyers electronically and in print locally and nationally to prosthetists, physical therapists, clinicians, and amputee support groups, b) expanding our

outreach to the public by producing video reports in local and national TV outlets as well as advertising in magazines targeted at amputee population such as *iMotion,* c) establishing contacts with prominent clinicians and centers involved in providing care to amputees, such as Walter Reed National Military Medical Center (Dr. Paul Pasquina), the Tampa VA Medical Center (Dr. Jeffery Heckmen), and OrthoCarolina (a private medical practice specializing in limb loss), educating them about our inclusion criteria and participation timeline, and distributing our recruitment materials.

On the technical side, our team has been successfully advancing the required technology for the study and productively working with existing participants to collect data. We have a strong presence in scientific conferences and meetings by either presenting our research findings or organizing sessions related to sensory neuroprostheses.

Changes that had a significant impact on expenditures

Despite the pandemic, we prioritized alternative work in this project as described in previous sections. Because the first implant surgery was delayed, our expenditure rate for this reporting period is lower compared to the previous report. However, the spending rate will increase as soon as we successfully complete our implant surgery. We fully expect to have unexpended funds available at the end of the study period and anticipate requesting a no-cost extension to complete the project as outlined in the SOW in spite of these unforeseen circumstances.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Shell, C. E., Christie, B. P., Marasco, P. D., Charkhkar, H., & Triolo, R. J. (2021). Lower-Limb Amputees Adjust Quiet Stance in Response to Manipulations of Plantar Sensation. *Frontiers in Neuroscience*, 15, 118. (Published). The federal support through this award was acknowledged.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers and presentations.

Our team member, Dr. Charkhkar, moderated and presented in the following sessions:
1) "Sensorimotor Neuroprosthetics: Are We Ready for Widespread Clinical Application?", *Neural Interfaces 2021: The NANS-NIC Joint Meeting*, Jun. 25-26, 2021
2) "Technologies to Restore Sensory Feedback after Lower-Limb Amputation", *10th International IEEE/EMBS Conference on Neural Engineering (NER'21)*, May 4-6, 2021

Additionally, two abstract submissions to the *International Society for Prosthetics and Orthotics (ISPO) 18th World Congress* were accepted for poster and podium presentations, respectively. The event will take place virtually November 1-4, 2021.

- **Website(s) or other Internet site(s)**

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

- **Other Products**

The link to the PBS NewsHour video:

https://www.youtube.com/watch?v=9vtcmZai3yI&ab_channel=PBSNewsHour

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Ronald Triolo
Project Role: PI
Researcher Identifier (e.g. ORCID ID): 0000-0003-0984-5803
Nearest person month worked: 1
Contribution to Project: Programmatic, administrative and scientific oversight of all aspects of the project

Name: Hamid Charkhkar
Project Role: Co-investigator (Technical)
Researcher Identifier (e.g. ORCID ID): 0000-0001-5485-5969
Nearest person month worked: 1
Contribution to Project: Conducting sensory stimulation tests, including stimulus calibration and parameter setting, psychometric testing, system integration and outcome measurement

Name: Melissa Schmitt (Clinical)
Project Role: Nurse Coordinator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Regulatory reporting and compliance, medical monitoring and clinical services

Name: Aarika Sheehan (Clinical)
Project Role: Physical Therapist
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Subject recruiting, candidate screening, functional training and outcome assessment

Name: Jeremy Dunning (Technical)
Project Role: Electrical Engineer
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Circuit design and software development for interfacing with Genium prosthesis

Name: Suzhou Li
Project Role: PhD Student (Technical)
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Designing and performing experiments to characterize effects of sensory neuroprosthesis in responding to slips and trips

Name: Daekyoo Kim
Project Role: Postdoctoral Fellow (Technical)
Researcher Identifier (e.g. ORCID ID): 0000-0002-6123-2900
Nearest person month worked: 1
Contribution to Project: Designing and conducting balance and gait assessments and analyzing biomechanical data from participants using sensory neuroprosthesis

Name: Jillian Vala
Project Role: Biomedical Engineer (Technical)
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Develop computer code for upcoming experiments. Assist in conducting experiments to assess effects of sensory feedback

Name: John Schnellenberger (Technical)
Project Role: Biomedical Engineer
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Circuit design and software development for home-going system

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Organization Name: Ottobock
Location of Organization: Vienna, Austria
Partner's contribution to the project: Industrial partner and collaborator. Ottobock provided us with a Genium Knee prosthesis on load without charge, and will lend technical assistance with accessing internal sensor data of the Genium device.

Organization Name: Case Western Reserve University
Location of Organization: Cleveland, OH
Partner's contribution to the project: Access to microfabrication, electronic design and circuit testing facilities, and technical support required for external stimulator design modifications and fabrication.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: